



Mini Review

Effect of Wnt signaling pathway on wound healing

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ABSTRACT

Wnt signaling pathway has been divided into two subclasses: the canonical pathway (Wnt/ β -catenin pathway) and the non-canonical pathway. It has been proven that Wnt/ β -catenin pathway can enhance wound healing, and some glycoprotein of Wnt family may directly or indirectly improve wound healing.

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The wound healing response has long been recognized as a complex process requiring the dynamic interaction of cellular and blood-borne elements. Many cellular, extracellular, vascular, and cytokine-related components interact with one another during the three major phases of wound healing; the inflammatory response, proliferative phase and remodeling phase [1].

At a molecular level, the relation between Wnt signaling pathway and wound healing have been described. Wnt signaling pathway has been divided into two subclasses: the canonical pathway (Wnt/ β -catenin pathway) and the non-canonical pathway [2].

β -Catenin and wound healing

β -Catenin is elevated in mesenchymal cells during the proliferative phase [3] and are believed to regulate dermal fibroblast proliferation rate, motility and invasiveness [4]. The proliferative phase of wound healing involves epithelialization, angiogenesis, and a provisional matrix formation (days 4–14). Activated platelets and macrophages stimulate epithelial proliferation through transforming growth factor- α (TGF- α) and epidermal growth factor EGF [5]. Which stimulated murine dermal fibroblast cultures have been shown to express increased β -catenin protein levels and T cell factor/lymphoid enhancer factor (TCF/LEF) mediated transcriptional activity as a result of GSK-3 β inactivity [6]. The accumulated β -catenin enters the nucleus, forms complexes as a co-factor with TCF/LEF transcription factors, and then triggers transcription of a set of target genes, which ultimately leads to regulation of cell proliferation and cell fate as well as cell transformation [7–9].

Recent data has shed further light on the interactions between TGF- β and β -catenin in cutaneous wound healing. Injuries could induce transient TGF- β signaling as observed during wound healing and this stimulation subsequently increases the level of β -catenin as shown here in desmoids cells and has been shown in wound healing. In the case of chronic injuries, this would reoccur and the cells would have repeated periods of β -catenin accumulation due to activation of TGF- β pathway. Accumulation of β -catenin continues until one susceptible cell finally gains a selective mutation [10,11]. TGF- β exerts its biological effects through TGF- β I and TGF- β II receptors, which form a heteromeric complex to facilitate signaling [12]. The activated type 1 TGF- β receptor phosphorylates Smads 2 and 3, which in turn interact with Smad4, resulting in nuclear translocation and activation of target gene transcription. Interestingly, full-thickness incisional wounding of Smad3 null mice results in an enhanced rate of re-epithelialization associated with a reduction in the number of fibroblasts, leading to an overall decrease in wound size [13–15]. Cheon et al. have recently demonstrated that this phenotype is dependent on β -catenin expression, because stabilized β -catenin expression reverses the Smad3 null effect on wound size. TGF- β -mediated fibroblast proliferation and hyperplastic wound formation was also shown to be dependent on β -catenin expression, demonstrating the central role of this molecule in the healing process [16] and highlighting the negative effects of β -catenin dysregulation. Macrophages (via IL-1 and TNF- α) and fibroblasts via (fibroblast growth factor-2) KGF-2 and TGF- β mediate angiogenesis through keratinocyte-stimulated release of vascular endothelial growth factor (VEGF), which is a significant promoter of endothelial proliferation and angiogenesis [17,18].

β -Catenin has long been established as a component of adherens junctions in association with cadherins. Adhesion proteins include epithelial cadherin (E-cadherin), neural cadherin

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(N-cadherin), placental cadherin (P-cadherin), muscle cadherin (Mcadherin), and vascular endothelial cadherin (VEcadherin or CDH5). While E-cadherin is the best characterized cadherin component of adherens junctions [19]. Adherens junctions allow for cell–cell adhesion, and when required, can disassemble to allow cell migration [20], a process important in the wound healing response [3].

The open wound bed eventually closes by wound contracture and the migration of epithelial cells from the wound edge. In contrast to the fibroblast response, β -catenin inhibits migration of human epithelial cells in culture [21] and, as normal epithelial cell differentiation and proliferation in wounded β -catenin null mice demonstrates, it is not an essential component of the epithelium for wound healing [22]. When the wound healing response is dysregulated, a variety of epithelial and mesenchymal disorders can occur. Fibroproliferative disorders, characterized by excessive proliferation of mesenchymal cells, range in severity from hypertrophic scars to neoplasms such as aggressive fibromatosis (desmoid tumors). These conditions display cellular and biochemical features that are remarkably similar to those involved in wound healing [3]. β -catenin links transmembrane E-cadherin to the actin cytoskeleton through β -catenin as well as other catenin molecules such as plakoglobin (or β -catenin) [23,24]. Adherens junctions allow for cell–cell adhesion, and when required, can disassemble to allow cell migration [20], a process important in wound healing response [3].

Current data showed that members of Wnt signaling were expressed in human fetal skin and human epidermal stem cells and Wnt/ β -catenin signaling was activated in human epidermal stem cells. And Wnt3a protein promoted the proliferation and inhibited differentiation of human epidermal stem cells in vitro. The Wnt3a/ β -catenin pathway is important for self renewal potential of stem cells [25].

Non-canonical signaling and wound healing

The Wnt/Ca²⁺ pathway is suggested to antagonize the canonical Wnt/ β -catenin pathway [26–28]. It is known that Wnt/Ca²⁺ pathway activated by Wnt5a activates Ca²⁺/calmodulin-dependent protein kinase II (Cam- KII) [29,26,30]. Blocking the activity of CamKII also inhibits primary endothelial cell proliferation. And endothelial cell proliferation was inhibited in the presence of the CamKII inhibitor KN-93. The Wnt/Ca²⁺ pathway plays a role in regulating endothelial cell proliferation, which was induced by treatment with recombinant Wnt5a [31]. Taken together, these suggest that Wnt5a acts on endothelial cells through an autocrine loop. Further more endothelial cell proliferation was inhibited when these cells were co-cultured with Wnt1 expressing cells [32].

Wnt5a signalling and Wnt/Ca²⁺ pathway are also known to control cell migration, although whether they promote or suppress cell motility seems to depend on cell type [32–35]. Wnt5a/Ca²⁺ signalling is also involved in regulating endothelial cell migration. Wnt5a mRNA is up-regulated in human primary endothelial cells in response to inflammatory mediator stimulus suggests that Wnt5a signalling pathway may play a role in inflammatory angiogenesis [36].

Wnt5a-mediated non-canonical signalling regulates human endothelial cell proliferation and migration. It may have a role in inflammation induced angiogenesis, thus indicating the Wnt non-canonical signalling network has the potential to play an important role in the regulation of endothelial cell fate and therefore in vascular remodeling [36].

The canonical and non-canonical Wnt pathways are likely to have opposing effect on endothelial cells, and probably antagonize each other in order to finely balance endothelial cell growth. In addition, VEGF and placenta growth factor (PIGF) have been suggested to regulate angiogenesis through an autocrine pathway

[37]. And VEGF is able to reverse the inhibitory effect of Wnt5a antibody in endothelial cell proliferation [36].

Wnt-inducible secreted protein-1 (WISP-1) was found to be induced within 72 h in organ-cultured human saphenous vein. While it is members of the PDGF superfamily, WISP-1 is closely related to connective tissue growth factor. During vascular wound repair, WISP-1 may recruit vascular smooth muscle cells (VSMCs) [38].

Wnt signaling is also a part of normal skin development. Skin injury induces Wnt signaling at 19.5 day of the embryo but not at earlier gestational ages associated with scarless repair, suggesting that Wnt signaling may play a role in fetal scarring [39].

Wnt is a kind of glycoprotein, which is organic compound composed of both a protein and a carbohydrate joined together in covalent chemical linkage. They are prevalent and important in mammalian tissues. The carbohydrate portion of a glycoprotein is usually a small sugar or no more than 8–10 individual monosaccharide units. Combinations of up to seven of the many different sugar molecules known to occur in nature comprise the saccharide portions of mammalian glycoproteins. The linkage between the oligosaccharide and the protein occurs by formation of a chemical bond to only one of four protein amino acids [40].

Further research

Human can get monosaccharide from diets and it is the basic composition of the glycoprotein, so adjusting the proportion of different kinds of monosaccharide in human body may change the concentration of the Wnt. On the other hand, there are many different kinds monosaccharide in the Wnt family; some members of this family have the relationship with wound healing. Increasing some specific monosaccharide will probably improve the Wnt family glycoprotein which has positive effect on the tissue restoration, or decreasing the class of glycoprotein which has negative indirect or direct effect on the wound healing.

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